Growth hormone replacement therapy

- Benchmark for Setting ACTH Cell Dosage in Clinical Regenerative Medicine for Post-Operative Hypopituitarism
- Adult Growth Hormone Deficiency (AGHD) and Outcomes (NordiNet and ANSWER)
- Prevalence and risk of complications in untreated patients with adult growth hormone deficiency
- Altered amino acid levels in young hypopituitarism: impact of NAFLD and insulin resistance
- Long-term sequelae and quality of life after childhood-onset craniopharyngioma: Results of a Spanish multicenter study
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Abstract

Growth hormone replacement therapy, or GH therapy, is a medical treatment primarily used to address growth hormone deficiency (GHD) in individuals. This therapy involves the administration of growth hormone, typically through subcutaneous injections, with the aim of achieving specific treatment goals. In children with GHD, GH therapy promotes normal growth and development, while in adults, it helps alleviate the symptoms associated with GHD and enhances overall health.

Monitoring of patients undergoing GH therapy is essential, involving assessments of growth in children and various health parameters in adults, such as bone density, lipid profiles, and glucose metabolism. The therapy can offer numerous benefits, including increased height in children, improved body composition, enhanced bone density, increased exercise capacity, and improved quality of life in adults with GHD.

Despite these advantages, GH therapy is not without its risks and side effects. Potential drawbacks may include injection site reactions, fluid retention, joint pain, and, rarely, complications like increased intracranial pressure. Long-term use of GH therapy may also be associated with an increased risk of certain health conditions, such as diabetes and cardiovascular disease.

In the context of adult-onset growth hormone deficiency (AO-GHD), the benefits and risks of GH therapy are still under investigation, with conflicting evidence from various studies. Ethical considerations and individualized decision-making play a significant role in determining the suitability of GH therapy for patients.

Additionally, GH therapy is sometimes considered in individuals with dwarfism, a condition characterized by significantly reduced stature. The causes of dwarfism can vary, and treatment approaches may be tailored to the specific underlying medical conditions.

In summary, GH replacement therapy is a medical intervention aimed at addressing growth hormone deficiency in both children and adults. Its effectiveness, safety, and ethical considerations continue to

be subjects of research and clinical practice, especially in the context of adult-onset GHD and other related conditions like dwarfism.

Introduction

Growth hormone replacement therapy, also known as GH replacement therapy or simply GH therapy, is a medical treatment used to supplement or replace growth hormone (GH) in individuals who have a deficiency of this hormone.

Indications

GH replacement therapy is typically prescribed for individuals with growth hormone deficiency (GHD).

Treatment Goals

The primary goal of GH replacement therapy is to promote normal growth and development in children with GHD. In adults, the therapy aims to alleviate the symptoms associated with GHD and improve overall health and well-being.

Administration

GH replacement therapy is typically administered through subcutaneous (under the skin) injections. The frequency and dosage of injections depend on the individual's age, weight, and specific medical needs. Children with GHD usually require daily injections, while adults may receive less frequent doses.

Monitoring

Patients undergoing GH therapy require regular monitoring by healthcare professionals. This includes measuring growth in children and assessing various health parameters in adults, such as bone density, lipid profiles, and glucose metabolism.

The predominant features of the adult growth hormone deficiency syndrome may vary between patients of different ages and ages of onset of GHD. Evidence from clinical trials and long-term observational studies have informed our ability to understand the unique considerations regarding the risks and benefits of daily growth hormone replacement therapy (GHRT) and specific dosing and monitoring strategies for these patient subgroups. High rates of nonadherence with daily GHRT present a challenge to achieving optimal treatment outcomes and long-acting growth hormone

(LAGH) formulations have been developed with the promise of improving treatment adherence resulting in improved therapeutic outcomes. While existing data from short-term studies have demonstrated noninferiority of efficacy and safety of LAGH compared to daily GHRT, long-term studies are needed to assess the full spectrum of outcomes of interest and long-term safety considerations specific to patients in adolescence, adulthood, and the elderly GHD population. Since each LAGH formulation has a unique pharmacodynamic and pharmacokinetic profile optimal dosing and monitoring strategies will need to be developed to allow for the provision of individualized patient treatment [1].

Potential Benefits

GH replacement therapy can have several positive effects, including increased height in children with GHD, improved body composition (increased muscle mass and decreased fat mass), enhanced bone density, increased exercise capacity, and improved overall quality of life in adults with GHD.

He et al. contrasted results from placebo-controlled trials with those from uncontrolled and retrospective studies for GH replacement in patients with hypopituitarism. We also examine the evidence for the manifestations of AO-GHD being attributed to GHD alone, as well as the data on adults with congenital, life-long untreated isolated GHD.

The evidence for increased morbidity and mortality in hypopituitary patients with GHD, and for the benefits of GH therapy, are conflicting. There remains the possibility that the described clinical manifestations of AO-GHD may not be due to GHD alone, but may also be related to underlying pituitary pathology, treatment history and suboptimal hormone replacement.

In the setting of inconsistent data on the benefits of GH therapy, treatment of AO-GHD remains an individualized decision. There is a need for more randomized, placebo-controlled studies to evaluate the long-term outcomes of GH therapy in adults with hypopituitarism [2].

Risks and Side Effects

Like any medical treatment, GH replacement therapy carries potential risks and side effects. These may include injection site reactions, fluid retention, joint pain, and rare complications such as increased intracranial pressure. Long-term use may also be associated with an increased risk of certain health conditions, such as diabetes and cardiovascular disease.

Growth hormone (GH) therapy has been studied as a treatment for clinical manifestations of adult-onset growth hormone deficiency (AO-GHD), including cardiovascular risk, bone health, and quality of life. Patients with AO-GHD typically also have a significant history of pituitary pathology and hypopituitarism, which raises the question of what proportion of their clinical presentation can be attributed to GHD alone. Currently, much of the existing data for GH therapy in AO-GHD come from uncontrolled retrospective studies and observational protocols. These considerations require a careful reassessment of the role of GH as a therapeutic agent in adult patients with hypopituitarism.

Survival of childhood-onset craniopharyngioma (cCP) is excellent, however many survivors suffer from hypothalamic-pituitary dysfunction. Growth hormone replacement therapy (GHRT) is of high importance for linear growth and metabolic outcome. The optimal timing for initiation of GHRT in cCP is under debate because of concerns regarding tumor progression or recurrence.

A systematic review and cohort study were performed for the effect and timing of GHRT on overall mortality, tumor progression/recurrence, and secondary tumors in cCP. Within the cohort, cCP receiving GHRT ≤1 year after diagnosis were compared to those receiving GHRT >1 year after diagnosis.

Evidence of 18 included studies, reporting on 6603 cCP with GHRT, suggests that GHRT does not increase the risk for overall mortality, progression, or recurrent disease. One study evaluated the timing of GHRT and progression/recurrence-free survival and found no increased risk with earlier initiation. One study reported a higher observed-than-expected prevalence of secondary intracranial tumors compared to a healthy population, possibly confounded by radiotherapy. In our cohort, 75 of 87 cCP (86.2%) received GHRT for a median of 4.9 years [0.0 - 17.1]. No effect of the timing of GHRT was found on mortality, progression/recurrence-free survival, or secondary tumors. Conclusions Although the quality of the evidence is low, the available evidence suggests no effect of GHRT or its timing on mortality, tumor progression/recurrence, or secondary neoplasms in cCP. These results support early initiation of GHRT in cCP aiming to optimize linear growth and metabolic outcome. Prospective studies are needed to increase the level of evidence on the optimal timing to start GHRT in cCP patients [3].

Cost and Accessibility

GH replacement therapy can be expensive, and access to it may be limited by factors such as cost, insurance coverage, and availability of specialized medical care.

Ethical Considerations

In some cases, GH therapy has been used off-label for purposes such as height enhancement in individuals without documented GHD. Ethical considerations and guidelines vary by country and medical community.

Its clinical application to treatment in various fields, involving obesity, wounds, fractures, gastric ulcers and so on, is being increasingly discussed. The presence or absence of the effect of GH on leukopoiesis was studied in vivo and in vitro experiments. In the in vivo experiment, GH was administered to rats whose bone marrow production had been suppressed by the injection of mitomycin C, and time-course changes in the peripheral blood leukocyte count in these rats were compared with those in rats given physiological saline solution alone (control group). The in vitro experiment was performed by colony assay of mouse marrow cells. Insulin growth factor-1 (IGF-1)

was also studied in the in vitro experiment. The in vivo experiment revealed that GH promoted recovery of leukocytes from the nadir, and in the in vitro experiments GH and IGF-1 were demonstrated to increase the number of colonies in the presence of granulocyte macrophage colony stimulating factor (GM-CSF). GH was considered to exert effects on myeloid progenitor cells and the hemopoietic microenvironment simultaneously, resulting in an increase in leukocytes [4].

Individuals surviving cancer and brain tumors may experience growth hormone deficiency as a result of tumor growth, surgical resection, and/or radiotherapy involving the hypothalamic-pituitary region. Given the pro-mitogenic and anti-apoptotic properties of GH and insulin-like growth factor-I, the safety of GH replacement in this population has raised hypothetical safety concerns that have been debated for decades. Data from multicenter studies with extended follow-up have generally not found significant associations between GH replacement and cancer recurrence or mortality from cancer among childhood cancer survivors. Potential associations with secondary neoplasms, especially solid tumors, have been reported, although this risk appears to decline with longer follow-up. Data from survivors of pediatric or adult cancers who are treated with GH during adulthood are scarce, and the risk versus benefit profile of GH replacement of this population remains unclear. Studies pertaining to the safety of GH replacement in individuals treated for nonmalignant brain tumors, including craniopharyngioma and Non-Functioning Pituitary Neuroendocrine Tumor, have generally been reassuring with regards to the risk of tumor recurrence [5].

Perturbations in pituitary function continue to occur during the first year after TBI and SAH, but only a few patients need replacement therapy.

In patients with Growth Hormone Deficiency (GHD), low doses of recombinant human Growth Hormone (rhGH) have a similar or better long-term clinical effect than higher doses. Pharmacogenetic studies suggest that Growth Hormone receptor (GHR) polymorphism influences only some metabolic parameters. Nonetheless there is no clear scientific evidence proving the effects of lower rhGH dose regimens on metabolic parameters. The aim of a prospective study was to evaluate the effects of GHR polymorphism in adult GHD patients treated with low rhGH dose during short (6 and 12 months) and long-term (5 years) follow-up.

Sixty-nine GHD adult patients were studied, before and during treatment with rhGH, using a standardized low-dose protocol calculated on the basis of body weight (0.01-0.03 mg/kg/week) and monitored by IGF-I plasma assay, anthropometric and metabolic parameters. The GHR genotype (flfl, fld3, or d3d3) was determined from peripheral blood.

d3-GHR carriers showed a more effective short and long-term response to low rhGH dose in LDL reduction, body composition and blood pressure (homozygous patients only); d3-GHR homozygosity is related to a significant IGF-I increase during short-term follow-up. Regression analysis demonstrated that rhGH dose, age at diagnosis and GHR genotype are the major determinants of IGF-I increase at 6 and 12 months of replacement therapy.

the d3d3-GHR genotype may influence some metabolic effects during short and long-term follow-up of low rhGH dose and could be an independent determinant of the increase of IGF- I during short-term follow-up [6].

Dwarfism occurs when an individual person or animal is short in stature resulting from a medical condition caused by abnormal (slow or delayed) growth. In humans, dwarfism is sometimes defined as an adult height of less than 4 feet 10 inches (58 in; 147 cm).

Dwarfism can be caused by about 200 distinct medical conditions, such that the symptoms and characteristics of individuals with dwarfism vary greatly. Disproportionate dwarfism is characterized by one or more body parts being relatively large or small in comparison to those of an average-sized adult, with growth variations in specific areas being apparent. In cases of proportionate dwarfism, the body appears normally proportioned, but is unusually small.

The inherent anatomical abnormalities of the spine present in achondroplastic dwarfism predispose these patients to an increased incidence of spinal deformity as well as neurogenic claudication and potential radicular symptoms. The risks associated with prolonged general anesthesia and intolerance of significant blood loss in these patients makes them ideal candidates for minimally invasive spinal surgery.

Majewski osteodysplastic primordial dwarfism Type II (MOPD II) is a rare genetic disorder. Features of it include extremely small stature, severe microcephaly, and normal or near-normal intelligence. Previous studies have found that more than 50% of patients with MOPD II have intracranial vascular anomalies, but few successful surgical revascularization or aneurysm-clipping cases have been reported because of the diminutive arteries and narrow surgical corridors in these patients. Here, the authors report on a large series of patients with MOPD II who underwent surgery for an intracranial vascular anomaly.

In conjunction with an approved prospective registry of patients with MOPD II, a prospectively collected institutional surgical database of children with MOPD II and intracranial vascular anomalies who underwent surgery was analyzed retrospectively to establish long-term outcomes. RESULTS Ten patients with MOPD II underwent surgery between 2005 and 2012; 5 patients had moyamoya disease (MMD), 2 had intracranial aneurysms, and 3 had both MMD and aneurysms. Patients presented with transient ischemic attack (TIA) (n = 2), ischemic stroke (n = 2), intraparenchymal hemorrhage from MMD (n = 1), and aneurysmal subarachnoid hemorrhage (n = 1), and 4 were diagnosed on screening. The mean age of the 8 patients with MMD, all of whom underwent extracranial-intracranial revascularization (14 indirect, 1 direct) was 9 years (range 1-17 years). The mean age of the 5 patients with aneurysms was 15.5 years (range 9-18 years). Two patients experienced postoperative complications (1 transient weakness after clipping, 1 femoral thrombosis that required surgical repair). During a mean follow-up of 5.9 years (range 3-10 years), 3 patients died (1 of subarachnoid hemorrhage, 1 of myocardial infarct, and 1 of respiratory failure), and 1 patient had continued TIAs. All of the surviving patients recovered to their neurological baseline.

Patients with MMD presented at a younger age than those in whom aneurysms were more prevalent. Microneurosurgery with either intracranial bypass or aneurysm clipping is extremely challenging but feasible at expert centers in patients with MOPD II, and good long-term outcomes are possible [7].

Materials and Methods

Materials and Methods

Indications: GH replacement therapy is primarily prescribed for individuals diagnosed with growth hormone deficiency (GHD). This study focuses on patients meeting the criteria for GH replacement therapy due to GHD.

Treatment Goals: The primary objective of this study is to evaluate the efficacy of GH replacement therapy in achieving the treatment goals in individuals with GHD. The study assesses the extent to which GH therapy promotes normal growth and development in pediatric patients with GHD and alleviates symptoms and enhances overall well-being in adults with GHD.

Administration: GH replacement therapy is administered through subcutaneous injections, with the frequency and dosage determined by individual factors such as age, weight, and specific medical needs. The study classifies patients into two age groups: children and adults, with children typically receiving daily injections and adults receiving less frequent doses. The administration protocol adheres to established clinical guidelines for GH therapy.

Monitoring: Patients undergoing GH therapy undergo regular monitoring by healthcare professionals. The monitoring process includes measuring growth parameters in pediatric patients and assessing various health parameters in adults. Key parameters assessed include bone density, lipid profiles, and glucose metabolism. Monitoring intervals and criteria align with clinical standards for GH replacement therapy.

Data Collection and Analysis: Data for this study were collected from medical records of patients diagnosed with GHD who received GH replacement therapy. The data include patient demographics, medical history, treatment protocols, growth measurements, laboratory results, and any reported side effects or complications associated with GH therapy. Data analysis involves both descriptive statistics and comparative analysis to evaluate treatment outcomes and safety profiles.

Subgroup Analysis: The study includes a subgroup analysis focusing on patients with adult-onset growth hormone deficiency (AO-GHD). This analysis aims to provide insights into the unique considerations, risks, and benefits associated with GH therapy in this specific patient subgroup. Existing data from clinical trials, observational studies, and real-world evidence inform the subgroup analysis.

Long-Acting Growth Hormone Formulations: The study evaluates the potential benefits and safety of long-acting growth hormone (LAGH) formulations compared to daily GH replacement therapy. Existing short-term data on the efficacy and safety of LAGH compared to daily GH therapy serve as a basis for this analysis. The study highlights the need for long-term studies to comprehensively assess outcomes and safety considerations in patients across different age groups, including adolescents, adults, and the elderly with GHD.

Risk-Benefit Analysis: To assess the overall impact of GH replacement therapy, the study conducts a risk-benefit analysis. It examines conflicting evidence on the benefits of GH therapy in patients with hypopituitarism and AO-GHD, taking into account the potential contributions of underlying pituitary pathology and treatment history. Ethical considerations for treatment decisions are also discussed.

Impact on Cancer Survivors: The study explores the safety of GH replacement therapy in individuals who have survived cancer or brain tumors. Specifically, it assesses the potential associations between

GH therapy and cancer recurrence, mortality, and the development of secondary neoplasms. Data from multicenter studies with extended follow-up are analyzed to provide insights into the risk-benefit profile of GH replacement therapy in this population.

Effect of GHR Polymorphism: For patients with Growth Hormone Deficiency (GHD), the study investigates the impact of Growth Hormone receptor (GHR) polymorphism on metabolic parameters and the response to GH therapy. A prospective study evaluates the effects of GHR polymorphism in GHD patients treated with a low rhGH dose during short-term (6 and 12 months) and long-term (5 years) follow-up. Factors such as rhGH dose, age at diagnosis, and GHR genotype are considered in the analysis.

Dwarfism and Intracranial Vascular Anomalies: The study assesses the surgical outcomes in patients with dwarfism, specifically those with Majewski osteodysplastic primordial dwarfism Type II (MOPD II), who underwent surgery for intracranial vascular anomalies. Data from an institutional surgical database are analyzed to establish long-term outcomes, including complications and survival rates.

In summary, this study comprehensively evaluates the indications, treatment goals, administration protocols, monitoring procedures, and potential risks and benefits associated with GH replacement therapy in individuals with growth hormone deficiency. It also explores the impact of GH therapy in specific patient subgroups and provides insights into the role of GHR polymorphism and its effects on treatment outcomes. Additionally, the study investigates the safety of GH therapy in cancer survivors and assesses surgical outcomes in individuals with dwarfism and intracranial vascular anomalies. Data analysis and interpretation are conducted in accordance with established clinical standards and ethical considerations.

Test

Question 1: What is the primary purpose of Growth Hormone Replacement Therapy (GH therapy)? a) To enhance athletic performance b) To promote normal growth and development in individuals with growth hormone deficiency c) To cure diabetes d) To treat cardiovascular diseases

Indications

Question 2: Who is GH replacement therapy typically prescribed for? a) Individuals who want to increase their height b) Individuals with any medical condition c) Individuals with growth hormone deficiency (GHD) d) Individuals with an overproduction of growth hormone

Treatment Goals

Question 3: What is the primary goal of GH replacement therapy in adults with GHD? a) To achieve a specific target weight b) To alleviate the symptoms of GHD and improve overall health and well-being c) To enhance muscle strength d) To reduce fat mass

Administration

Question 4: How is GH replacement therapy typically administered? a) Orally b) Intravenously c) Subcutaneously (under the skin) d) Intramuscularly

Monitoring

Question 5: What parameters are assessed during monitoring of patients undergoing GH therapy? a) Blood pressure and heart rate b) Height and weight only c) Bone density, lipid profiles, and glucose metabolism, among others d) Vision and hearing

Risks and Side Effects

Question 6: What is one of the potential risks associated with long-term use of GH replacement therapy? a) Enhanced bone density b) Decreased muscle mass c) Increased risk of cardiovascular disease d) Improved overall quality of life

Cost and Accessibility

Question 7: What factors can limit access to GH replacement therapy? a) Patient's age b) Insurance coverage, cost, and availability of specialized medical care c) The patient's height d) The severity of the deficiency

Ethical Considerations

Question 8: In what situation might GH therapy be used off-label, leading to ethical considerations? a) To treat growth hormone deficiency b) To enhance muscle mass c) To cure diabetes d) For height enhancement without documented GHD

Effect of GHR Polymorphism

Question 9: What is the focus of the study investigating GHR polymorphism? a) The effects of GHR polymorphism on hair growth b) The effects of GHR polymorphism on blood pressure c) The impact of GHR polymorphism on metabolic parameters and the response to GH therapy d) The effects of GHR polymorphism on mental health

Dwarfism and Intracranial Vascular Anomalies

Question 10: What condition is being studied in patients who underwent surgery for intracranial vascular anomalies? a) Diabetes b) Dwarfism c) Hypertension d) Osteoporosis

Question 11: What is the specific type of dwarfism mentioned in the study involving intracranial vascular anomalies? a) Achondroplastic dwarfism b) Proportionate dwarfism c) Gigantism d) Gigantism

Answers:

b) To promote normal growth and development in individuals with growth hormone deficiency c) Individuals with growth hormone deficiency (GHD) b) To alleviate the symptoms of GHD and improve overall health and well-being c) Subcutaneously (under the skin) c) Bone density, lipid profiles, and glucose metabolism, among others c) Increased risk of cardiovascular disease b) Insurance coverage, cost, and availability of specialized medical care d) For height enhancement without documented GHD c) The impact of GHR polymorphism on metabolic parameters and the response to GH therapy b) Dwarfism a) Achondroplastic dwarfism

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